Published in final edited form as:

Hum Immunol. 2000 March ; 61(3): 326–333.

HLA Class II Haplotype Associations with Inflammatory Bowel Disease in Jewish (Ashkenazi) and Non-Jewish Caucasian Populations

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Abstract

Ulcerative colitis (UC) and Crohn's disease (CD) are the clinical entities comprising idiopathic inflammatory bowel disease (IBD). Previous studies on the association of IBD and human leukocyte antigen (HLA) class II genes suggested a role for HLA in this disease. Here we present HLA class II (DRB1, DQB1, DQA1, DPB1) allele and haplotype distributions determined using the polymerase chain reaction and sequence-specific oligonucleotide probe methods. A total of 578 UC and CD Caucasian patients and controls from Jewish (Ashkenazi) and non-Jewish populations was examined. Our previously reported association of DR1–DQ5 with CD was attributable to DRB1*0103. A dramatic association with IBD and the highly unusual DRB1*0103-DQA1*0501-DQB1*0301 haplotype (OR = 6.6, $p = 0.036$) was found. The more common DR1 haplotype, DRB1*0103-DQA1*0101-DQB1*0501, was also associated with IBD (OR = 3.1, $p = 0.014$), a result suggesting that interaction between DR and DQ may determine the extent of disease risk. Our previously reported association of DR2 with UC was attributable to DRB1*1502 (OR = 2.6, $p = 0.006$). At the DPB1 locus, a significant association of DPB1*0401 with CD was observed for the combined populations (OR = 1.85, $p = 0.007$). These observations indicate that some class II alleles and haplotypes confer susceptibility to both UC and CD, implying common immunogenetic mechanisms of pathogenesis, while others confer risk to only one of these diseases, and illustrate the value of DNA HLA typing in disease susceptibility analyses.

Keywords

IBD; Crohn's disease; ulcerative colitis; HLA class II association

Introduction

Inflammatory bowel disease (IBD) consists of two clinical entities, ulcerative colitis (UC) and Crohn's disease (CD). These chronic idiopathic inflammatory diseases of the gastrointestinal tract are considered together because of their overlapping clinical, epidemiologic, and pathogenetic features, and shared complications and therapies. The common symptoms of UC and CD are diarrhea, abdominal pain, fever, and weight loss. However, UC and CD can usually be distinguished by clinical and pathologic characteristics. Chronic inflammation of the colonic and rectal mucosa with relapses and remissions of rectal bleeding characterize UC. Inflammation in CD may occur anywhere in the gastrointestinal tract, but the most common form is ileocolitis, affecting both the small bowel and the colon. In rare cases, it is difficult to diagnose either UC or CD, in which case the term *indeterminate colitis* is used to define what may perhaps be a third form of IBD.

Although infectious agents may trigger the onset of disease and the immune system mediates pathogenic tissue damage, genetic factors appear to determine the susceptibility of a given individual, based on racial and ethnic differences in disease incidence. For example, IBD is more prevalent among Jews than among non-Jews [1, 2]. In addition, the familial clustering of both UC and CD indicates a genetic predisposition to these two forms of IBD. Based on the pattern of familial aggregation, one might expect that some genes predispose to one or the other of these diseases, whereas some genes might confer the risk of both.

Recent genetic studies to identify specific IBD susceptibility genes have focused on genome-wide scans with anonymous DNA markers, providing some evidence of susceptibility loci on chromosomes 3, 7, and 12 [3], and chromosome 16 [4, 5]. Linkage analyses demonstrated evidence of the linkage of both CD and UC to regions flanked by microsatellite markers on chromosomes 3, 7, and 12 (lod score 5.47) [3]. Other studies support the linkage of CD to a region on chromosome 16, with no contribution to UC susceptibility [4, 5]. A recent study using nonparametric analyses of microsatellites in the region of the tumor necrosis factor (TNF) on chromosome 6 supported the linkage of CD with the major histocompatibility complex (MHC) region [6]. Immunoregulatory genes, such as the cytokine genes (TNF and IL-1ra), the complement genes, and cell adhesion molecule (CAM) genes, have also been analyzed for an association with IBD (reviewed in [7]). Analysis of the cytokine gene markers IL-1RA allele 2 and TNF- α (-308) suggest only a very modest to no association in IBD patients versus controls [8–11]. Other studies have shown, however, a TNF- α (a2b1c2d4e1) and DR1-DQ5 extended haplotype association [12], and linkage and association between the HLA and TNF genes in Crohn's disease [6]. Yang et al. estimated that the MHC region contributes a maximum of 33% of the total increased risk in sibs over the population risk of Crohn's disease [6]. These observations are consistent with the disease heterogeneity in CD and UC, and with the predicted model that UC and CD share some susceptibility loci but differ at others.

Analysis of candidate genes with known immunologic function include the HLA class II genes, T-cell receptor genes, and immunoglobulin genes. The HLA class II genes, which have been associated with IBD in several studies [5–7, 13–16], are plausible candidate genes because they play a fundamental role in peptide binding and T-cell receptor repertoire determination, and have been associated with various autoimmune and infectious diseases (reviewed in [17]). Finally, data from a number of experimental models of IBD indicate that HLA class II-restricted CD4⁺ T cells play a critical immunoregulatory role in IBD, and are essential to the regulation of intestinal immune responses [18].

While not all previous studies of the association of IBD and HLA class II genes have proved concordant, these inconsistencies may be due to sampling size, inadequate typing methods, inappropriate controls, and/or perhaps genetic heterogeneity of the patient populations. For example, from earlier investigations using serologic methods, the frequency of the HLA class II serotype was increased in UC patients versus controls in most but not all European and United States Caucasian populations [7, 13, 15, 19–22]. In an English population study using DNA typing methods Satsangi et al. found no association with DR2 in CD or UC patients [14]. However, three studies in Japanese populations using DNA typing methods indicated that DRB1*1501 showed a protective association with CD [23], and DRB1*1502 showed an association with UC [16, 24]. In other serologic studies, the HLA class II DR1-DQ5 haplotype was found to be associated with CD in Caucasians [12, 15, 25]. Moreover, recent molecular analyses of the HLA class II genes in Japanese [16, 23, 24] and Caucasian populations [13, 26–28] (including the current study) demonstrated significant HLA class II allele and haplotype associations with IBD.

Due to inconsistencies in the results of analyses of such complex, polygenic disorders as IBD, larger data sets are required. Even when a relatively strong genetic component is

observed, as assessed by relative risk to siblings or twin concordance data, large databases are necessary to help compensate for statistical difficulties due, for example, to ethnic variation in allele frequency and disease heterogeneity. To increase our understanding of the etiology and pathogenesis of various forms of IBD, we performed molecular HLA class II analysis (DRB1–DQB1–DPB1) on a large number of samples from both Jewish (Ashkenazi) and non-Jewish Caucasian subjects with IBD (CD, UC, or IBD indeterminate), and ethnically matched, normal control subjects. In our previous studies, we performed overall HLA disease association analyses with IBD [19, 26, 29]. The results of these studies suggested that particular HLA class II alleles or serogroups were associated with IBD. Because of these prior hypotheses, we collapsed the analysis in the current study, and examined in particular the association of subtypes of DR1 with DQ, subtypes of DR2, and the DPB1*0401 association, with CD, UC, or IBD as a whole.

Materials and Methods

Study Subjects

Patients with CD, UC, or IBD indeterminate were ascertained from the clinical IBD program at Cedars-Sinai Medical Center or referred by the Crohn's and Colitis Foundation of America. The diagnoses were based on conventional endoscopic, histologic, and clinical criteria [30]. Informed consent was obtained from all participants and the study protocols were approved by the Cedars-Sinai Medical Center Human Subjects Protection Committee. Patient and control samples were obtained from Jewish Ashkenazi Caucasian and non-Jewish Caucasian populations, including simplex and multiplex families. To increase ethnic compatibility, control samples were selected from spouses or friends of the patients. An individual was used as a control only if he/she did not have IBD, multiple sclerosis, systemic lupus erythematosus, or an other recognized autoimmune disease. The distribution of age and sex was comparable in patients and controls. Table 1 lists the study subjects by ethnicity and disease.

HLA Typing

Genomic DNA was extracted using the QIAGEN (Valencia, CA, USA) QIAamp 96 Spin Kit from long-term cell lines established from the IBD patient and control samples. DNA samples were typed at the HLA class II loci (DRB1, DQA1, DQB1, and DPB1) using the polymerase chain reaction to amplify a locus-specific second exon product, and analyzed using sequence-specific oligonucleotide probes in a dot blot format, as previously described [31–36].

Class II haplotypes (DRB1–DQA1–DQB1) were inferred from linkage disequilibrium patterns [37, 38], unequivocally determined by homozygosity, or deduced from pedigree analyses. Haplotypes with unusual DR-DQ associations or rare alleles were confirmed by typing informative family members, when available.

Statistical Methods

Comparisons of MHC class II allele frequencies between CD, UC, or IBD combined (including CD, UC and IBD indeterminate) patients and controls were tested by the Pearson

χ^2 test. Data from Ashkenazi Jewish and nonJewish subjects was analyzed first by stratification for ethnicity, and then by combining the groups. In cases in which one of the expected counts was less than 5, p value was calculated based on Fisher's two-tailed exact test. When there was a similar trend in the Jewish and nonJewish groups, a stratified analysis was conducted using the Mantel-Haenszel method to obtain point estimates (that is, OR) tests of significance (that is, p values), and 95% confidence intervals for the stratified combined sample [39]. Reported p values were not adjusted by the number of comparisons. All analyses were done using Statistical Analysis Software, version 6.12 (SAS Institute, Inc., Cary, NC, USA).

Results

DR1

The results of the HLA class II DRB1*01 haplotype IBD association analyses of the combined Caucasian Jewish and non-Jewish IBD patient and control samples are shown in Table 2. Our previously reported association of DR1–DQ5 with CD [12, 15, 19, 26] occurred as a trend in the present study (OR = 1.5, p = 0.068). However, the DR1 association was found attributable to the subtype DRB1*0103 in the combined Caucasian group of IBD patients, and this subtype was also significantly associated with both CD and UC patients (IBD: OR = 4.6, p = 0.001; CD: OR = 4.4, p = 0.002; and UC: OR = 4.9, p = 0.001). DRB1*0101 and DRB1*0102 were not associated with IBD (UC, CD, or IBD indeterminate) in these populations.

Haplotype analysis revealed a dramatic association with the highly unusual DRB1*0103–DQA1*0501–DQB1*0301 haplotype. This haplotype, inferred in 16 IBD patients, one control, and confirmed in one of one informative pedigree (Fig. 1), was significantly associated with IBD (OR = 6.9, p = 0.034), and with UC (OR = 8.6, p = 0.018) in the combined populations. In addition, the patient-to-control ratio (P/C) of haplotype frequencies, a parameter related to absolute risk, is very high (7.1 for this rare haplotype) in these samples (see Discussion). This rare haplotype appears to have been generated by a recombination event between DRB1 and DQA1.

The more common DRB1*0103 haplotype, DRB1*0103–DQA1*0101–DQB1*0501, was also associated with IBD (OR = 3.5, p = 0.007), with CD (OR = 3.3, p = 0.015) and with UC (OR = 3.8, p = 0.007). OR and P/C are considerably lower (3.2) for this more common DRB1*0103–DQB1*0501 haplotype than for the very rare DRB1*0103–DQB1*0301 haplotype, suggesting that both the DR and DQ molecules are involved in conferring risk.

DR2

HLA class II DRB1*15 alleles and IBD association analysis results for the combined Ashkenazi and non-Ashkenazi Caucasian populations are shown in Table 3. We confirmed our previously reported association of DR2 with UC [19], found here attributable to the subtype DRB1*1502 (OR = 2.6, p = 0.006). In our analysis, no other DR2 subtype was found to be associated with IBD, UC, or CD. The great majority of DRB1*1502 alleles were

in association with DQB1*0601 (91.2%), while the majority of the DRB1*1501 alleles were associated with DQB1*0602 (89.8%).

Unusual DRB1*04 and DRB1*11 Haplotypes

HLA class II DRB1*04 haplotype and IBD association analyses revealed a rare haplotype, DRB1*0404 – DQA1*0301–DQB1*0402, which was inferred in 8 patients and confirmed in two of two informative pedigrees (Fig. 2). This unusual haplotype was observed in 7 CD patients, 1 UC patient, and 2 control subjects. Another unusual haplotype, DRB1*1104 – DQB1*0603, shows a trend for protective association in IBD patients (OR = 0.15, p = 0.058).

DPB1*0401

At the DPB1 locus, an association of DPB1*0401 with CD was observed (OR = 1.6, p = 0.015). After stratification for ethnicity, the susceptibility association of the DPB1*0401 allele was significant in the non-Ashkenazi CD patients (OR = 1.81, p = 0.014), but it did not attain significance in the Ashkenazi CD patients (OR = 1.3, p = 0.384).

Discussion

Our analysis of HLA class II allele and haplotype association with IBD in this case-control study suggests that only specific subtypes of disease associated DR serotypes appear to confer risk. Previous studies implicated the serotype DR1 as a risk factor for CD [12, 26]. In the current study, however, DRB1*0103, but not other DR1 types, shows an association with CD, as well as with UC (Table 2). DRB1*0103 differs from the other DR1 alleles by an LLEQR to ILEDE change at codon positions 67–71 in exon 2. These polymorphic residues participate in the DR molecule pockets numbers 4 and 7 of the peptide binding groove, and may be involved in binding a disease-related peptide. We had previously noted the DR1–DQ5 association in Jewish and non-Jewish Caucasian CD patients [12, 26]. Several other groups have identified a DR1 association to IBD/CD in Caucasians in the United States [15], France [25], and the Netherlands [9]. The recent study of Satsangi et al. from Japan using DNA typing also indicates a significant association with the DRB1*0103 allele and UC in the Japanese population [14]. Clearly, typing methods capable of distinguishing DR1 subtypes are critical for revealing this association, and demonstrating that DRB1*0103 is associated with both CD and UC. Furthermore, populations with a very low frequency of DRB1*0103 may not show a DR1 association with IBD.

DRB1*0103 has a distinct pattern of serologic reactivity, known as DR-Bon, and can sometimes be distinguished from other DR1 types. The highly unusual DR-Bon specificity was also found independently by one of us (D.T.) in 7 of 11 Caucasian IBD patients. Four of these patients had the DR-Bon-DQ7 (DQB1*0301) serologically defined haplotype, and the remainder had the DQ5 serotype. Based on the data reported here, it appears that specific combinations of DR and DQ alleles determine the extent of risk for IBD. The highly unusual haplotype DRB1*0103–DQB1*0301 confers a higher risk for both CD and UC than does the more common haplotype, DRB1*0103–DQB1*0501. The patient-control ratio, which is a parameter related to absolute risk, is 7.1 for DRB1*0103–DQB1*0301, versus 3.2 for

DRB1*0103–DQB1*0501. The observation that specific combinations of DR and DQ alleles are necessary to determine disease risk has also been found for DR4 susceptibility to insulin-dependent diabetes mellitus [40, 41] (reviewed in [17]). The disease association of the DRB1*0103 allele on two different DR–DQ haplotypes suggests that this allele may be directly involved in disease risk, and not serve simply as a marker in linkage disequilibrium with some other disease gene.

Polymorphisms in non-HLA genes within the MHC have also been suggested to be associated with IBD [8–10, 12]. Some MHC markers may be associated due simply to linkage disequilibrium with other disease-related MHC genes. Alternatively, there may be several different genes within the MHC that contribute to disease risk. The DR1–DQ5 haplotype was found to be in linkage disequilibrium with the TNF microsatellite haplotype TNFa2b1c2d4e1 associated with Crohn's disease [6, 12]. In addition, Bouma et al. found that the HLADR1 and TNF-I haplotype in a Dutch population had low TNF- α secretion, the low secretor phenotype, resulting in less inflammation and tissue damage [9]. Although these findings suggest that the DR and TNF markers on chromosome 6 define strong genetic risk factors for IBD, and for CD in particular, based on our current data it is not clear whether disease severity is due to linkage with different TNF subtypes or to the underlying DRB1*01 subtype in these populations. Our data, which underscore the importance of HLA-DNA typing in disease association studies, indicates DRB1*0103 as the disease risk allele and not other DR1 subtypes, which include DRB1*0101 and *0102.

The DR2 serotype has been associated with UC in some but not all studied populations [13, 15, 19–22]. Our previously reported association of DR2 with UC [19] was found here attributable only to DRB1*1502 (Table 3). In two recent studies from Japan, DRB1*1502 was associated with susceptibility as well as progression to UC [16, 24]. Another study indicates that the DRB1*1501 allele confers protection from CD in Japanese [23]. The DRB1*1501 and DRB1*1502 alleles differ by only one amino acid at residue position 86 of exon 2 in the DRB1 gene. DRB1*1501 has a valine (V–86) and *1502 a glycine (G–86) at this position. The DR β chain residue at codon position 86 is within pocket number 1, and is known to control the DR $\alpha\beta$ dimer stability and influence peptide selection [42]. The V–86 and G–86 dimorphism is highly conserved in DR β chains in all populations. Thus, the presence of glycine at residue 86 may play a role in the association of DRB1*1502 with UC. We also note that DRB1*0103 carries Gly at codon position 86.

DRB1*1502 is also in linkage disequilibrium with different DQB1 alleles than are other DR15 alleles. The most commonly associated DQB1 allele with DRB1*1502 among Caucasians as well as Japanese was DQB1*0601 (91.2% in our data set), while the most common DQB1 association with DRB1*1501 was DQB1*0602 (89.8% in our data set). The amino acid differences between DQB1*0601 and *0602 include codon positions 9, 28, 30, 37–38, and 66–67. All of these amino residue changes correspond to pocket 7 or 9, which participates in peptide presentation and recognition. Thus, the differential disease risk for DRB1*1502 versus DRB1*1501 could be attributed either to DRB1 residue 86, to the various differences between the DQB1 alleles, or to both. In addition, it cannot be excluded that the disease association of DRB1*1502–DQB1*0601 reflects linkage disequilibrium with some other gene.

The observed disease association with the DRB1*0103 and DRB1*1502 alleles, and with the relevant DRB1-DQB1 haplotypes, emphasizes the need for high-resolution HLA-DNA typing in IBD disease association studies. These associations could be missed at the level of serologic typing, or in populations in which these disease-associated subtypes are very rare or absent.

Although the rare DRB1*0404–DQA1*0301–DQB1*0402 haplotype (Figure 2) was increased in our CD patients, it did not attain statistical significance ($OR = 2.7$, $p = 0.2$). Two recent studies of Japanese CD patients, however, indicated a significant association with DQB1*0402 [16, 23]. In those studies, DQB1*0402 was linked to DRB1*0410, which was also associated with CD. DRB1*0404 and DRB1*0410 differ by an aspartic acid to a serine amino acid change at codon position 57, which is within pocket number 9 of the peptide binding groove. It appears likely that DR4 – DQB1*0402 haplotypes confer increased risk for CD, but the evaluation of the role of the DRB1*0404–DQB1*0402 haplotype in CD susceptibility in Caucasians and the relative contributions of the DR and DQ molecules requires further study. A protective trend was found with another unusual haplotype, DRB1*1104 – DQB1*0603, although this negative association with IBD did not attain significance ($OR = 0.15$, $p = 0.058$). Because of the very low frequency of these DR-DQ haplotypes, more precise assessment of their susceptibility or protective effects with IBD will require further studies with larger sample sizes.

Finally, the DPB1*0401 association with CD observed for these populations ($OR = 1.56$, $p = 0.015$) was, following stratification on ethnicity, significant only in the non-Jewish CD patients ($OR = 1.8$, $p = 0.014$). DPB1*0401, therefore, does not appear to be a risk factor among Ashkenazi Jewish CD patients ($OR = 1.3$, $p = 0.384$). These data also provide further evidence of genetic heterogeneity between CD and UC, and underscore the notion that disease association patterns of certain alleles depend on the ethnic group tested and, presumably, on the genetic background of the populations studied.

Conclusions

Results of our analysis of HLA class II allele and haplotype distributions in Caucasian Jewish and non-Jewish IBD patients and controls suggest that the HLA class II allele DRB1*0103 confers susceptibility to IBD, both ulcerative colitis and Crohn's disease. Further, because the rare DRB1*0103–DQB1*0301 haplotype appears to confer greater risk than the more common DRB1*0103–DQB1*0501 haplotype, interaction between DR and DQ may be involved in determining the extent of risk. A significant association with DRB1*1502 and ulcerative colitis was also identified in these populations. A modest increased risk for DPB1*0401 was observed, and was specific only to the non-Jewish population. Our observations support the role of the MHC in IBD, and indicate that some class II alleles and haplotypes confer susceptibility to both ulcerative colitis and Crohn's disease, implying common immunogenetic mechanisms of pathogenesis, while others confer the risk of only one of these diseases. This study illustrates the potential of HLA and disease association analyses to identify previously unreported or rare haplotypes, and the value of DNA-based typing for detecting disease-associated subtypes. Although not definitive in the diagnosis of disease, these genetic studies of HLA class II alleles and haplotypes in IBD

patients may be useful in the identification of predisposed individuals, as well as in the stratification of patients. Genetic differences may also be predictors of drug responsiveness, which could help to enhance the statistical power of a clinical trial.

Acknowledgments

This work was supported by National Institute of Health grants DK46763 and DK54967. The authors would like to thank the patients, their families, and referring physicians for their support in our ongoing genetic studies of inflammatory bowel disease. We would also like to thank the Cedars-Sinai Board of Governors Chair in Medical Genetics (J.I.R.) for their support.

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Abbreviations

CAM	cell adhesion molecule
CD	Crohn's disease
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
MHC	major histocompatibility complex P/C patient-to-control ratio
TNF	tumor necrosis factor
UC	ulcerative colitis

Figure 1.

Segregation of DRB1*0103–DQA1*0501–DQB1*0301 haplotype in a family with IBD. The highly unusual DRB1*0103–DQA1*0501–DQB1*0301 haplotype, inferred in 16 IBD patients, one control, and confirmed in one of one informative pedigree as illustrated, was significantly associated with IBD (OR = 6.9, $p = 0.034$), and with UC (OR = 8.6, $p = 0.018$) in the combined populations. In this pedigree, the affected mother and proband son both carry this rare DR1 haplotype. This rare haplotype appears to have been generated by an uncommon recombination event between DRB1 and DQA1.

Figure 2.

Segregation of DRB1*0404–DQA1*0301–DQB1*0402 haplotype in a family with IBD. HLA class II DRB1*04 haplotype and IBD association analyses revealed a rare haplotype, DRB1*0404–DQA1*0301–DQB1*0402, which was inferred in 8 patients and confirmed in two of two informative pedigrees, of which one is illustrated. In this pedigree, the affected mother and proband daughter both carry the unusual DRB1*04–DQB1*0402 haplotype. This unusual haplotype was observed in 7 CD patients, 1 UC patient, and 2 control subjects.

Table 1
Study subjects by ethnicity and type of IBD

	Number of Subjects		
	Jewish	Non-Jewish	Combined
CD	125	179	304
UC	114	156	270
IBD Indeterminate	2	2	4
IBD Total	241	337	578
Control	78	154	232

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease

Table 2

DR1 in combined Jewish and non-Jewish ethnicities

	Control (n=232)		IBD (n=578)				CD (n=304)				UC (n=270)			
	%	n	%	n	p	OR	95%	CI	%	n	p	OR	95%	CI
DR1	18.1	42	24.7	143	0.026	1.5	1.1	2.3	25.3	77	0.027	1.6	1.1	2.5
DQ5	28.5	66	31.7	183	0.294	1.2	0.9	1.7	32.6	99	0.237	1.3	0.9	1.8
DR1-DQ5	17.7	41	22.8	132	0.068	1.4	1	2.1	23.4	71	0.068	1.5	1	2.3
DRB1*0101	10.8	25	9.9	57	0.977	1	0.6	1.6	10.2	31	0.938	1	0.6	1.8
DRB1*0102	5.2	12	7.4	43	0.379	1.3	0.7	2.6	8.2	25	0.237	1.5	0.8	3.1
DRB1*0103	2.2	5	8.3	48	0.001	4.6	1.9	11	7.9	24	0.002	4.4	1.8	11.2
DRB1*0103-DQA1*0501-DQB1*0301	0.4	1	2.8	16	0.034	6.9	1.2	40.1	2.3	7	0.076	5.7	0.8	38.9
DRB1*0103-DQA1*0101-DQB1*0501	2.2	5	6.4	37	0.007	3.5	1.4	8.7	5.9	18	0.015	3.3	1.3	8.8

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease

Table 3

DR2 in combined Jewish and non-Jewish groups

	Control (n=232)			IBD (n=578)					CD (n=304)					UC (n=270)				
	%	n		%	n	p	OR	95%	CI	%	n	p	OR	95%	CI	%	n	p
DR2	26.7	62		28	162	0.487	1.1	0.8	1.6	23	70	0.46	0.9	0.6	1.3	33.7	91	0.045
DRB1*1501	19	44		18.3	106	0.844	1	0.7	1.5	17.4	53	0.886	1	0.6	1.5	19.6	53	0.584
DRB1*1502	4.7	11		7.4	43	0.2	1.6	0.8	3.1	3.6	11	0.435	0.7	0.3	1.7	11.9	32	0.006
DRB1*1601	3	7		2.1	12	0.457	0.7	0.3	1.8	1.6	5	0.321	0.6	0.2	1.8	2.2	6	0.646
DRB1*1602	0	0		0.5	3	—	—	—	—	0.3	1	—	—	—	—	0.7	2	—

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease